Alternating Multiblock Amphiphilic Copolymers of PEG and Tyrosine-Derived Diphenols. 1. Synthesis and Characterization

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ABSTRACT: We describe the synthesis and characterization of a new family of strictly alternating multiblock polyethers based on poly(ethylene glycol) (PEG) and the tyrosine-derived diphenols, desaminotyrosyl-tyrosine alkyl ester (DTR). These polymers are referred to as poly(DTR-PEG ether)s. The PEG and DTR units are linked through a hydrolytically stable ether bond, combining an extremely hydrophilic with an extremely hydrophobic unit within the polymer backbone. The resulting copolymers are amphiphilic in nature. Interfacial and solution polymerization methods were evaluated for this synthesis. Interfacial reaction failed to yield multiblock polymers, while solution polymerization afforded poly(DTR-PEG ether)s containing approximately 4−8 repeat units. PEG blocks of molecular weights ranging from 1000 to 8000 and alkyl pendent chains (R) ranging from ethyl (C2) to dodecyl (C12) were used to vary the molecular structure of the multiblock copolymers. The melting behavior of the poly(DTR-PEG ether)s was studied by modulated differential scanning calorimetry in the heat-only mode. Results indicate that the PEG units in the copolymers melt independently and that the DTR units act as impurities, causing melting point depression and reduced crystallinity. The surfactant properties of poly(DTR-PEG ether)s are described in part 2 of this series of reports.

Introduction

Water-soluble amphiphilic molecules that are capable of forming hydrophobic domains in aqueous solutions are widely investigated.[1−5] Examples include Pluronics,[1] copolymers of poly(ethylene glycol) (PEG) and poly(dimethylsiloxane) (PDMS) or ϵ-caprolactone,[6,7] and a large numbers of dendrimers.[8] Most polymeric nonionic surfactants are random copolymers[4,9,10] or A−B and A−B−A type block copolymers.[1,3,11−14]

Architectures consisting of alternating blocks or groups have been used in supramolecular chemistry in order to induce self-organization through specific interactions between regularly spaced groups. As an example, synthetic molecules with alternating electron-rich and electron-deficient groups have been shown to fold in water.[15] Closely related to the work presented here are alternating copolymers of PEG and derivatives of the amino acid L-lysine. These copolymers were synthesized in this laboratory, and their solution behavior was studied in detail.[16,17] PEG−lysine copolymers with long (C18) pendent chains self-assemble into flowerlike micelles of 18 nm diameter, containing 12−18 hydrophobes. The incorporation in the backbone of a more hydrophobic moiety than lysine was expected to induce self-assembly without the need for long pendent chains, thereby allowing adjustment of the volume and micropolarity of micelles through variations of the polymer pendent chain. Thus, the purpose of this work was to obtain alternating, multiblock copolymers of PEG and a highly hydrophobic comonomer using a synthetic design that allowed for systematic changes in polymer composition.

The diphenolic monomer, desaminotyrosyl-tyrosine alkyl ester (DTR) (a derivative of the natural amino acid L-tyrosine), is currently used in a number of polymers synthesized in this laboratory for biomaterials applications.[18,19] In addition to being highly hydrophobic, the DTR unit (Figure 1) has the potential to participate in aromatic−aromatic interactions and hydrogen bonds, and the length of its alkyl pendent chain can be varied. Upon copolymerization of DTR monomers with activated PEG through an ether bond, strictly alternating multiblock copolymers, referred to as poly(DTR-PEG ether)s (Figure 1), were obtained.

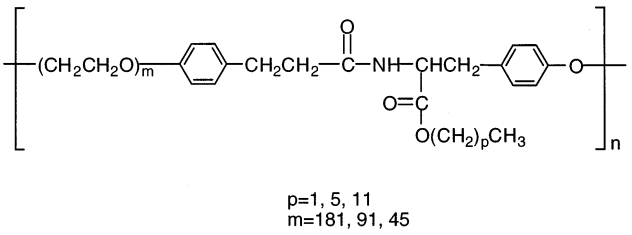

Figure 1. Structure of poly(DTR-PEG ether)s. DTR = desaminotyrosyl-tyrosine alkyl ester (see also Special Note on Nomenclature).

The polymer backbone of poly(DTR-PEG ether)s contains ether and amide bonds which are generally considered to be hydrolytically stable, unless exposed to drastic conditions. However, the pendent group (R) is attached to the backbone via a potentially cleavable ester linkage. The stability of this ester bond has been studied under physiological conditions (e.g., 37 °C in pH 7.4 phosphate buffered solution) and was found to degrade only very slowly.[20,21] On the basis of these studies, one can expect the polymer structure to be stable for several weeks in aqueous solutions as long as the pH is maintained around 7 and the storage temperature does not exceed 37 °C.

To explore the effect of molecular composition on the thermal properties of these polymers, both the length of the alkyl pendent chains and the molecular weight of the PEG unit were varied. The polymer structure was confirmed by ^{1}H and ^{13}C NMR, and the thermal behavior was studied by modulated differential scanning calorimetry (MDSC).

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Special Note on Nomenclature

We use three-digit abbreviations to designate the various polymer compositions. The first letter of this three-digit code indicates the alkyl pendent chain "R" linked to the DTR unit, where DTR stands for desaminotyrosyl-tyrosine alkyl ester (Figure 1). The three pendent chains "R" used are E = ethyl, H = hexyl, and D = dodecyl. The second digit is a number indicating the molecular weight of the PEG units, and the third digit is always the letter "K" to indicate that the molecular weight of the PEG units is measured in kDa (i.e., 2K = PEG_{2000}). Therefore, E2K stands for poly(DTE-PEG_{2000} ether).

Materials and Methods

Poly(ethylene glycol)s of molecular weights 1000, 2000, 4000, and 8000 were purchased from Fluka and were melt-dried prior to use. Methanesulfonyl chloride, triethylamine, tetrabutylammonium hydrogen sulfate, and thionyl chloride were purchased from Acros (a division of Fisher Scientific) and used fresh as received. Benzyltriethylammonium chloride (Aldrich) was also used as received. All solvents were HPLC grade. Acetonitrile was dried by distillation over calcium hydride. Toluene was dried by azeotropic distillation. Dimethyl sulfoxide and dimethylformamide were dried over 3 Å molecular sieves (Aldrich) prior to use. Powdered anhydrous potassium hydroxide and anhydrous potassium carbonate were weighed quickly, and traces of water were removed directly in the polymerization vessel by azeotropic distillation in toluene.

Synthesis of PEG Dichloride. 25 mmol of PEG was weighed in a 250 mL round-bottomed flask. The reaction vessel was equipped with a magnetic stirrer and an ice bath. 30 mL of thionyl chloride was added slowly through an addition funnel, then the mixture was allowed to reach room temperature, and the flask was equipped with a reflux condenser connected to a sodium hydroxide trap for the evolving hydrochloride vapors. The mixture was heated by means of an oil bath at 60 °C for 24 h. The product was isolated by precipitation with ethyl ether and purified by recrystallization from 2-propanol.

Synthesis of PEG Dimethanesulfonate. The preparation of PEG dimethanesulfonate was adapted from a previously published procedure by Harris and co-workers[22] for PEG ditosylate. 21.5 mmol of PEG was weighed into a 500 mL round-bottom flask equipped with a magnetic stirrer and dissolved in 80 mL of dichloromethane. The solution was cooled in an ice−water bath for 10 min, and then 15 mL (107.5 mmol) of triethylamine was added, followed by 8.3 mL (107.5 mmol) of methanesulfonyl chloride added through an addition funnel over a period of 30 min. The flask was kept at 4 °C for 14 h, and then the byproduct triethylammonium chloride was removed by filtration. The filtrate was concentrated, the filtration was repeated, and the product was isolated by precipitation with ethyl ether. Further purification of the product was achieved by suspending silica gel (1 g/g of PEG) and Norit pellets (0.1 g/g of PEG) in 30−50 mL of warm toluene and stirring for 15 min. The warm solution was clarified by filtration, and the product was precipitated with ethyl ether.

Synthesis of Desaminotyrosyl-tyrosine Alkyl Esters. Desaminotyrosyl-tyrosine alkyl esters (DTR) were prepared as previously described.[23]

Interfacial Polymerization with Phase-Transfer Catalysis. Equimolar amounts of diphenol and PEG dichloride or PEG dimethanesulfonate were reacted with vigorous overhead stirring in a water/organic biphasic solvent system in the presence of varying amounts of phase-transfer catalysts such as tetrabutylammonium hydrogen sulfate or benzyltriethylammonium chloride (10% mol/mol to 4-fold excess). The aqueous phase contained KOH, $NaHCO_3$, or borate buffer at pH 8.5. The reaction was carried out at room temperature with methylene chloride as the organic phase and at 50 °C in toluene. The reaction progress was monitored by gel permeation chromatography (GPC) in DMF/LiBr 0.1%. After 20 h the mixture was acidified to pH 3 with HCl 1 M, the layers were separated, and the aqueous phase was extracted three times with methylene chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated to dryness.

Table 1. Solution Polymerization of PEG2000 Dimesylate and DTE[a,b]

entry	solvent	base	reaction time[c]	M_n (Da)
1	CH_3CN	KOH	72 h	12000
2	toluene[d]	KOH	24 h	no reaction
3	toluene	KOH	4 days	small amount of dimer and trimer
4	toluene[e]	K_2CO_3	72 h	13500
5	toluene	K_2CO_3	4 days	16000

[a] Typical reaction conditions: equimolar amounts of activated PEG and diphenol, 20% molar excess of base, volume of solvent equal to weight of PEG2000 dimesylate, 65−70 °C, overhead stirring. [b] Molecular weight determined by GPC with DMF/LiBr 0.1% as the mobile phase, relative to PEG standards. [c] Time at which no further increase in molecular weight was observed by GPC. [d] Reaction carried out at reflux. [e] Reaction carried out at 90 °C.

Solution Polymerization. Specific reagents, solvents, and reaction conditions are shown in Table 1. In a typical experiment, a two-necked round-bottomed flask equipped with an overhead stirrer was charged with an equimolar amount of diphenol and PEG dimethanesulfonate of molecular weight 1000−8000. A 20% excess of base was added, and the reactants were dissolved or suspended in a volume of solvent equal to the weight of PEG derivative. The mixture was heated in an oil bath at 65−70 °C, and reaction progress was monitored by GPC. Upon dilution of the reaction mixture with dichloromethane a precipitate formed, which was separated by centrifugation, decanted, and discarded. The product in the supernatant was precipitated with ethyl ether and dissolved a second time in dichloromethane. An amount of silica gel equal to the weight of reacted PEG was suspended in the polymer solution, the slurry was shaken for 15 min, and then the silica was separated by centrifugation. The supernatant was decanted, and the product was isolated by precipitation with ethyl ether. The treatment with silica gel was repeated until no residual diphenol was detected by HPLC. HPLC analysis of a 1.5 mg/mL polymer solution showed no peaks corresponding to unreacted diphenols. On the basis of a detection limit of 10 μg/mL, 1 mg of polymer contains less than 6×10^{-3} mg of free diphenol.

Synthesis of α,ω-Bis(DTH)PEG2000. A 50 mL one-necked round-bottomed flask was charged with 0.225 g (4 mmol) of powdered anhydrous potassium hydroxide and 20 mL of toluene. The toluene was distilled in a Dean−Stark trap with reflux for 2 h to remove traces of water, then the residual solvent was removed under high vacuum, and the flask was filled with dry nitrogen. PEG2000 dimethanesulfonate (2 g, 1 mmol), DTH (1.65 g, 4 mmol), and 3 mL of dry acetonitrile were added while maintaining a gentle nitrogen stream, the flask was equipped with a reflux condenser and an overhead stirrer, and the mixture was heated with an oil bath at 65−70 °C for 3 days. The reaction crude was diluted with 40 mL of dichloromethane, and the solid byproducts were removed by vacuum filtration in a fritted glass funnel. The product was precipitated with 400 mL of ethyl ether and isolated by filtration at normal pressure. The solid was dried overnight under a nitrogen stream, and then it was dissolved in 10 mL of water and extracted three times with 5 mL aliquots of ethyl acetate. A small amount of sodium chloride was added during the extraction to brake the emulsion. The aqueous phase was back-extracted five times with 5 mL portions of methylene chloride; the organic phase was dried over magnesium sulfate, decanted, and concentrated to half its volume. The product was precipitated with 200 mL of ethyl ether, isolated by

filtration, and dried under a stream of nitrogen followed by high vacuum. No residual DTH was detected by HPLC. HPLC analysis of a 1.5 mg/mL polymer solution showed no peaks corresponding to unreacted DTH. Based on a detection limit of 10 μg/mL, 1 mg of polymer contains less than 6×10^{-3} mg of free DTH.

Polymerization of α,ω-Bis(DTH)PEG2000 and PEG2000 Dimethanesulfonate. A 20 mL glass vial was charged with α,ω-bis(DTH)PEG2000 (0.214 g, 0.078 mmol), PEG2000 dimethanesulfonate (0.164 g, 0.078 mmol), powdered anhydrous potassium hydroxide (13 mg, 0.234 mmol), and 0.5 mL of dry acetonitrile. The vial was sealed and shaken in a vortex mixer for 30 min until a uniform suspension was obtained, and then it was kept at 70 °C in a heated oven for 3 days with occasional shaking. The reaction mixture was diluted with 5 mL of dichloromethane, and the product was precipitated with 50 mL of ethyl ether and isolated by filtration at normal pressure. It was again dissolved in 2.5 mL of dichloromethane, and 0.25 g of silica gel was suspended in the polymer solution. The slurry was shaken for 15 min, then the solids were separated by centrifugation, and the supernatant was decanted and added dropwise to 30 mL of ethyl ether in order to isolate the product by precipitation and filtration. The polymer was analyzed by GPC.

Fractionation of Poly(DTH-PEG2K ether). Two molecular weight fractions were obtained from poly(DTH-PEG2K ether) synthesized by polymerizing α,ω-bis(DTH)PEG2000 and PEG2000 dimethanesulfonate. The fractionation was performed by size exclusion chromatography using a Perkin-Elmer 250 LC binary pump, two PL-gel columns (pore size 10^5 and 10^4 Å), a Waters 410 RI detector, and a Digital Venturis 466 computerized station using Millenium software. THF was chosen as the mobile phase for ease of solvent removal. The flow rate was1 mL/min. 200 μL aliquots of 2% polymer solution were injected, and two fractions were collected at different retention time intervals. Collection of the first fraction began at the onset of peak detection. A delay of 60 s between detection and elution was taken into account when collecting fractions. The molecular weight of the resulting fractions was determined by GPC with dimethylformamide/0.1% lithium bromide as the mobile phase, since this is a better solvent system for PEG copolymers.

Gel Permeation Chromatography (GPC). Molecular weights were determined by GPC using a Waters model 510 pump, two PL-gel columns (pore size 10^5 and 10^4 Å), a Waters 410 RI detector, and a Digital Venturis 466 computerized station using Millenium software. The mobile phase was dimethylformamide containing 0.1% lithium bromide at a flow rate of 0.8 mL/min. Molecular weights were calculated relative to poly(ethylene oxide) standards (Polymer Laboratories Inc., Amherst, MA).

HPLC. The presence of residual free diphenols in the polymer was checked by HPLC. The instrument consists of a Perkin-Elmer 410 LC pump, a 3 cm C18 column, a LC-235 diode array detector set at 220 nm, and a Turbochrom Navigator workstation version 6.1.1 (also from Perkin-Elmer). The mobile phase was a gradient of water/acetonitrile/trifluoroacetic acid 0.1%.

NMR. ^{1}H NMR spectra were obtained in a Varian Unity 300 spectrophotometer operating at a proton frequency of 300 MHz. ^{13}C NMR spectra were obtained in a Varian Gemini 200 spectrophotometer operating at a carbon frequency of 50 MHz.

Modulated Scanning Differential Calorimetry (MDSC). Thermal analysis was carried out using a 2920 modulated differential scanning calorimeter from TA Instruments operated with TA Advantage Control software version 2.6D for Windows NT. Data analysis was performed with TA Universal Analysis software version 1.0 for Windows NT. Nitrogen at a flow rate of 50 mL/min was used as the purge gas, and temperature control was achieved using the DSC RCS (refrigerated cooling accessory) from TA Instruments. The temperature was calibrated with the melting point of an indium standard, and the heat capacity constant was determined by calibration with a sapphire standard. 10−15 mg of sample was loaded in nonhermetic aluminum pans. An empty pan was used as reference. The samples were melted in the DSC at 80 °C for 10 min, and then the temperature was lowered to −40 °C at 5 °C/min. The analysis was carried out in the heat-only modulation mode with the following method: modulation of ±0.21 °C in a 40 s period, 5 min isothermal equilibration at −40 °C, 2° C/min ramp to 80 °C. The melting peaks were integrated with a linear baseline between manually defined peak limits, and the melting points were determined with the tangent method.

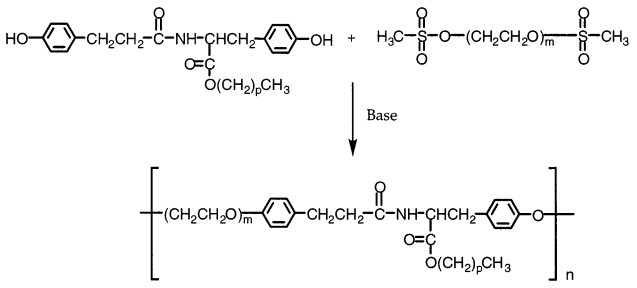


Figure 2. Synthetic scheme for poly(DTR-PEG ether)s by direct polymerization using either interfacial or solution polymerization conditions.

Results and Discussion

Synthesis of Poly(DTR-PEG ether). The synthesis of polyethers under mild reaction conditions presents several challenges since ether bond formation via aliphatic nucleophilic displacement is usually less than quantitative and requires drastic reaction conditions. For this reason, we explored several synthetic approaches.

(a) The Interfacial Approach. The interfacial approach failed when applied to the synthesis of poly(DTR-PEG ether)s using the reaction scheme shown in Figure 2. ^{13}C NMR spectroscopy showed hydrolysis of the leaving groups of PEG ($-CH_2OH$ peak at 61 ppm), thus supporting the hypothesis that the ether bond formation is simply too slow to allow polymerization in an aqueous basic environment.

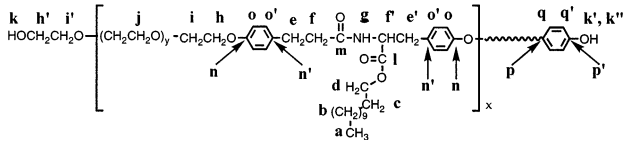
(b) Direct Solution Polymerization. The synthesis of poly(DTR-PEG ether)s was carried out in anhydrous aprotic solvents, where PEG end group and DTR ester hydrolysis are unlikely to occur. The same reaction scheme shown in Figure 2 was employed. DMF, DMSO, acetonitrile, and toluene were used in combination with either anhydrous K_2CO_3 or powdered, anhydrous KOH (Table 1). On the basis of the suitability of the reaction conditions for DTRs of different solubility, as well as of the ease of workup, we chose acetonitrile and anhydrous KOH for a synthetic method that would work irrespectively of the polarity and nature of the pendent chain of the DTR monomer. Copolymers of PEG of molecular weights 1000, 2000, 4000, and 8000 with DTE, DTH, and DTD were obtained, for a total of 12 polymers. The outcome of these syntheses is summarized in Table 2. The average number of PEG-DTR blocks per chain, as expressed by the degree of polymerization, DP, and the polydispersity remained constant, irrespective of the length of the PEG block or the nature of the pendent chain in DTR. As a consequence, polymers prepared from PEG blocks of higher molecular weight have a higher overall molecular weight. We determined that the methanesulfonation of PEG results in a PEG functionality of 98−99%. Assuming a conversion of 90−95% of the methanesulfonated PEG units to polymer, the well-known relationship (eq 1) between monomer conversion (P) and the average number (n) of

Table 2. Polyethers Obtained with the Solution Polymerization Method[a]

polymer	M_n[b] (Da)	polydispersity[b] (M_w/M_n)	yield (%)
E1K	4 900	1.7	50
H1K	4 400	1.6	50
D1K	5 300	1.9	50
E2K	12 100	1.7	60
H2K	14 400	2.3	60
D2K	12 500	1.8	60
E4K	19 800	2.0	60
H4K	14 600	1.9	60
D4K	16 300	1.9	60
E8K	44 400	2.0	50
H8K	34 100	1.9	50
D8K	34 100	1.9	50

[a] Reaction conditions: equimolar amounts of activated PEG and diphenol; 20% molar excess of powdered, anhydrous potassium hydroxide; volume of dry acetonitrile equal to weight of activated PEG; 65−70 °C; overhead stirring; reaction time = 72 h. [b]Molecular weights determined on the crude product.

Table 3. ^{13}C and ^{1}H NMR Data for Poly(DTD-PEG2K ether)



proton/carbon	^{13}C chemical shift (ppm)	^{1}H chemical shift (ppm)
a	13.94	0.92 (t)
b	22.49−29.44	1.31 (broad)
c	31.72	1.54 (broad)
d	65.44	4.04 (t)
e, e′	30.40, 38.21	2.41 (t), 2.72−2.92 (m)
f, f′	36.93, 53.0	2.59 (t), 4.44 (m)
g	N/A	8.34 (b)
h′	62.20	4.19 (m)
h	69.8−71.6	4.11 (t)
i, i′		3.75 (t), 3.69 (t)
j		3.4−3.6
k, k′, k″	N/A	4.44 (broad), 9.21−9.30 (d)
l	171.51	N/A
m	171.38	N/A
n	157.71	N/A
n′	132.82 (DAT) 129.11 (Tyr)	N/A
o	114.54 (DAT) 114.44 (Tyr)	6.90 (dd)
o′	130.1 (Tyr) 127.9 (DAT)	7.17 (dd)
p	130.1 (DAT) 127.9 (Tyr)	N/A
p′	157.14	
q	130.07 (Tyr) 127.9 (DAT)	6.73 (dd)
q′	115.36 (DAT) 114.10 (Tyr)	7.02 (dd)

repeat units per chain correctly predicts the experimentally found value of $n = 4-8$.

$$P = 1 - \frac{1}{2n} \qquad (1)$$

To confirm the molecular structure of all polymers prepared by this procedure, both ^{1}H and ^{13}C NMR spectra were obtained (Table 3). In particular, proton peaks a−d and g confirm the integrity of the ester pendent chain and the amide bond in the polymer backbone, which are potentially hydrolyzable bonds.

(c) Two-Step Solution Polymerization. An alternative approach to obtain higher molecular weight poly-

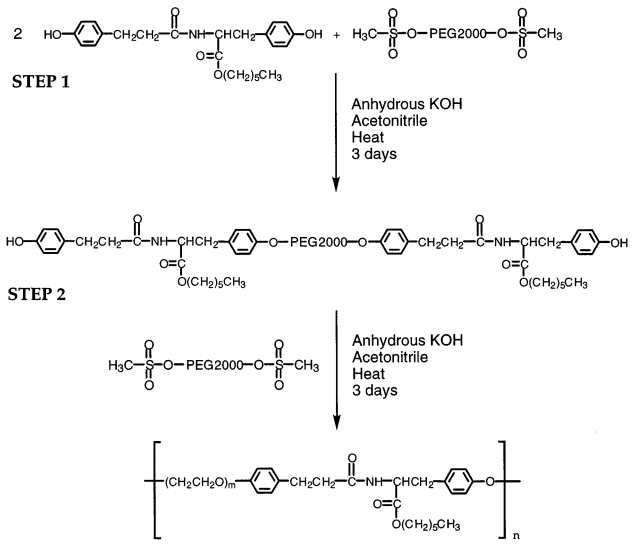


Figure 3. Two-step synthesis of poly(DTH-PEG2K ether).

(DTR-PEG ether)s is shown in Figure 3. In the first step, PEG2000 dimethanesulfonate was reacted with an excess DTH to obtain α,ω-bis(DTH)PEG2000. This trimer was then polymerized with an equimolar amount of PEG2000 dimethanesulfonate to yield the same structure as with the direct polymerization approach. The potential advantage of the two-step process is that two blocks (one PEG and one DTR) are added at each reactive step, whereas in the direct polymerization approach two reactive steps are needed in order to add two blocks. As a result, one would expect that, given the same degree of conversion, the two-step approach yields a polymer of approximately twice the molecular weight of that obtained by direct polymerization. Indeed, when this approach was applied to the synthesis of H2K, some high molecular weight polymer did form. However, the reaction was not clean, and a bimodal, non-Gaussian molecular weight distribution was obtained. Overall, the weight-average M_w was 52 000, but the number-average M_n was only 9000. Thus, the average chain length was smaller than in the one-step polymerization, and the polymer had a very high polydispersity (PDI) of 5.9. From the polydisperse polymer obtained, we isolated a high molecular weight fraction of $M_w = 116\,000$ and $M_n = 46\,000$, corresponding to 19 PEG-DTH blocks per average chain, by size exclusion chromatography in THF. The overall yield of this high molecular weight fraction was 15%.

Melting Behavior of Poly(DTR-PEG ether)s. Polymer melting is usually accompanied by recrystallization of the partially molten material.[24] The heat flow detected by conventional DSC results from the overlap of melting and recrystallization of the polymer, so that the outcome may be dependent on the experimental conditions. In modulated DSC (MDSC), a sinusoidal temperature−time dependence is overlapped with an underlying linear heating rate. With the appropriate choice of amplitude and period of the modulation, one can combine high instantaneous heating rates to increase sensitivity with low underlying heating rates to improve resolution. The amplitude and period of the modulation can also be adjusted to the underlying heating rate in such a way that the sample is heated at a periodically varying instantaneous heating rate, without being cooled during the melting process. In other words, the instantaneous heating rate varies between 0 °C/min and

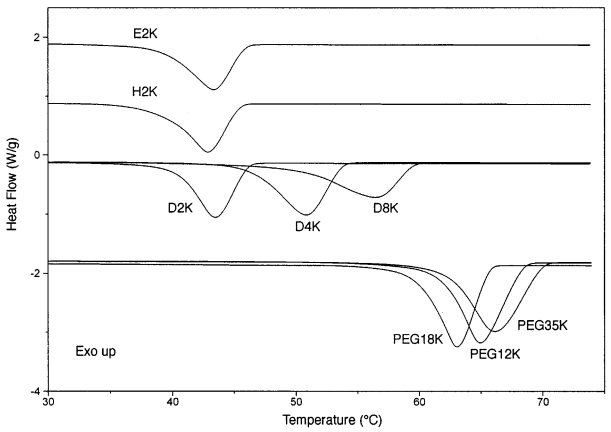


Figure 4. Melting of poly(DTR-PEG ether)s as observed by MDSC. PEG samples were also included in the study for comparison. Melting points and heats of fusion are presented in Table 4.

Table 4. Thermal Data for Selected Poly(DTR-PEG ether)s and Poly(ethylene glycol)s

polymer	peak melting point (°C)	heat of fusion[a] (J/g)	polymer crystallinity relative to semicrystalline PEG[b]
E2K	43	102	54
H2K	43	110	58
D2K	43	109	58
D4K	51	134	69
D8K	56	131	70
PEG2000	53	187	
PEG4000	61	194	
PEG8000	63	187	
PEG12000	65	187	
PEG35000	66	187	

[a] Heat of fusion per weight of PEG in the copolymer. [b] Based on the heat of fusion of the corresponding semicrystalline PEG determined in the same experimental conditions. For example, the value for PEG4000 is used for D4K.

a positive value, without assuming negative values at any point. This is referred to as the "heat-only modulation". By using heat-only modulation, no recrystallization is induced, resulting in more accurate measurements of onset, range of melting, and heat of fusion than conventional DSC.

We selected E2K, H2K, D2K, D4K, and D8K for a detailed study of the polymer melting behavior by heat-only MDSC (Figure 4). This selection included three polymers with the same PEG block length but different pendent chains and three polymers with the same pendent chains but different PEG blocks. For comparison, PEG blocks of varying molecular weight were also analyzed. The heat of fusion per gram of PEG (Table 4) in the copolymers was calculated from the integration of the melting peaks. The heats of fusion obtained for semicrystalline PEGs in our experimental conditions are in good agreement with literature values.[25,26] The melting points of all three copolymers of PEG2000 are identical within experimental error, thus showing that the length of the pendent chain does not have a significant effect on the melting of the poly(DTR−PEG ether)s. On the other hand, increasing the molecular weight of PEG from 2000 to 4000 increased the melting point from 43 °C for D2K to 51 °C for D4K. The melting point increase is less pronounced from D4K to D8K (51−56 °C). This trend was also observed for the melting points of PEG2000, PEG4000, and PEG8000. The expected difference in melting point due to the overall molecular weight of D2K and D4K would be much smaller, as can be deduced from the melting points of PEG12000 and PEG35000 (65 and 66 °C). E2K, H2K, and D2K exhibit similar crystallinity relative to PEG2000 (54−58%), while D4K and D8K show the same, higher value (69−70%) relative to PEG4000 and PEG8000, respectively.

In all cases the melting points of the copolymers are lower than the melting points of the corresponding pure PEG blocks, indicating that the PEG chains in the copolymers melt independently of each other and that the DTR units simply act as impurities, causing melting point depression and a decrease in crystallinity. The melting peak of D8K is much broader than the peaks of the copolymers containing PEG blocks of lower molecular weight. In fact, considering poly(DTR-PEG ether)s to be polymers of ethylene oxide (CH_2CH_2O) contaminated by DTR units, the mole fraction of "monomeric impurities" of DTR becomes extremely small as the molecular weight of the PEG blocks is increased. Copolymers of increasing PEG content can, therefore, be regarded as increasingly similar to pure poly(ethylene oxide). This approach explains the observed melting behavior of poly(DTR-PEG ether)s.

Conclusions

A new family of alternating polyethers, poly(DTR-PEG ether)s, based on PEG and the tyrosine-derived diphenol DTR was synthesized by direct solution polymerization. The preparation of these polyethers was a synthetic challenge that required a detailed study of the optimum reaction conditions. We were able to show that interfacial reaction conditions fail to yield the desired polymers, due to the competitive hydrolysis of the electrophilic PEG end groups. However, suitable solution polymerization conditions were found, resulting in polymers with identical degree of polymerization (DP) for PEG blocks of molecular weight 1000−8000 and DTR monomers with 2−12 carbon atoms in the alkyl chain "R". A two-step solution polymerization approach resulted in a polymer with a broad molecular weight distribution. Fractionation by size exclusion chromatography provided a very high molecular weight polymer from the polydisperse product.

The molecular weight of the PEG units in the copolymers was found to affect both the melting point and crystallinity of the materials, while no effect was observed from the pendent chain length. Results indicate that the PEG units melt as independent chains and that the DTR units act as impurities, lowering the melting point and crystallinity.

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